REMARKS

Amendments to the Claims

Claims 1-32 are pending. Claims 2, 8-12, 15, 16, 24-30, and 32 are withdrawn as being drawn to a non-elected invention. Accordingly, claims 1, 3-7, 13, 14, 17-23, and 31 are currently under consideration.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 3-7, 13, 14, 17-23 and 31 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Turner et al. (US 2004/0053876), Tuschl et al., (US 2004/0259247), Rana et al., (US 2005/0020521), Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Pieken et al. (Science, 1991, 253:314-317); Sullenger et al. (US 2003/0083294); Matulic-Adamic *et al.* (US 5,998,203); Braasch *et al.* (Biochemistry, 2002 Vol. 41:4503-4510), as evidenced by Caplen et al. (Expert Opinion Biol. Ther., 2003, 3:575-586). Applicants respectfully traverse the rejections.

The claims of the instant invention are directed to multifunctional siNA molecules comprising two separate oligonucleotides, wherein each oligonucleotide has an "antisense" region which is complementary to a different target sequence and which is also partially complementary with the antisense region of the opposite oligonucleotide. Certain of the claimed multifunctional siNA molecules comprise various chemical modifications.

Specifically, the claimed multifunctional siNA molecules have the formula:

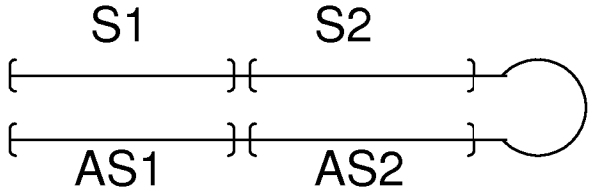
5'-p-X Z X'-3'
3'-Y'Z Y-p-5'

Each of the individual oligonucleotides (p-X Z X' and Y' Z Y-p) has a length between 24 and 38 nucleotides. Each of the individual oligonucleotides comprises a sequence that is complementary to a different target sequence, where the different target sequences can be sequences from different genes or can be different target sites on the same gene. The sequence that is complementary to a (first) target sequence in the p-X Z X' oligonucleotide is XZ (for the sake of convenience here, referred to as "antisense 1" or "AS1"). The sequence that is complementary to a (second) target sequence in the Y' Z Y-p oligonucleotide is ZY (for the sake

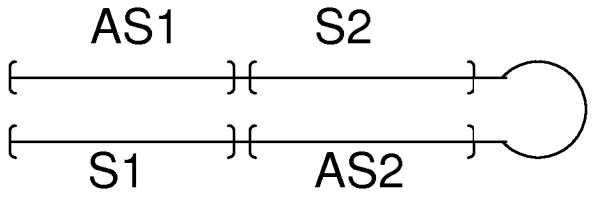
of convenience here, referred to as "antisense 2" or "AS2"). XZ and ZY (AS1 and AS2) share complementarity in the Z sequence region, which Z region comprises 1 to 24 nucleotides. The X sequence (part of AS1) comprises 1 to 21 nucleotides and is complementary to nucleotide sequence present in region Y'. The Y sequence (part of AS2) comprises 1 to 21 nucleotides and is complementary to nucleotide sequence present in region X'. This structure, comprising two "antisense" regions on separate oligonucleotides that are partially complementary to each other, is important to ensure antisense regions of sufficient length to bind their respective targets while maintaining an overall length that does not trigger the cellular interferon response.

In contrast to the present invention, Turner et al is directed to single-stranded hairpin siRNA molecules and methods of making and using the same, not to double-stranded siNA (ds siNA) molecules. According to Turner et al., the chemical synthesis of double-stranded siRNA is expensive (compared to the enzymatic synthesis of single-stranded siRNA) and, moreover, inducing cells to take up exogenous nucleic acids is difficult to achieve in some cells and results in short-term treatment. Therefore, the object of Turner et al. is to provide single-stranded hairpin siRNAs that can be enzymatically synthesized and produced inside a cell. As Turner et al. is designed to be enzymatically synthesized, the insertion of chemical modification as set forth in the claims of the instant application, e.g., 2-7, 13, 17-23 would not be viable. Moreover, there would be no motivation to combine any of the other references cited with the Turner et al. reference in this regard, as it would defeat the stated purpose of Turner et al., which is to have a hairpin that can be enzymatically synthesized and produced in a cell.

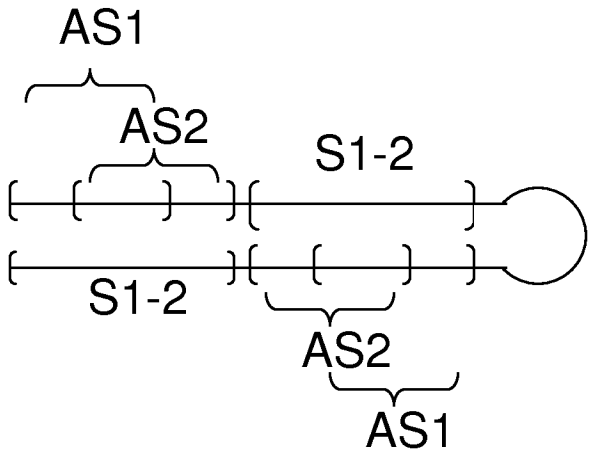
In one embodiment, the Turner et al. reference speculates that it might be possible to target more than one RNA with a single hairpin siRNA molecule and proposes several hairpin siRNA structures that may have this capability, none of which comprises the features of the presently claimed siNA molecules (see paragraph 218). For example, Turner et al. suggests a hairpin siRNA comprising at least two different non-overlapping antisense sequences, wherein each antisense sequence is from about 18 to about 29 nucleotides long. The non-overlapping antisense sequences can be adjacent to each other on one strand (as shown below).



Alternatively, the non-overlapping antisense sequences can be on separate strands of the hairpin siRNA (shown below). As depicted, Turner et al. envisions a single-stranded hairpin siRNA with an antisense sequence 1 on one strand and an antisense sequence 2 on another strand, wherein the antisense sequences are complementary with corresponding sense sequences on the opposite strands but not with each other.



Turner et al further contemplates that "any of the antisense sequences may also comprise a set of two overlapping antisense sequences". A schematic drawing of this structure is shown:



As depicted in each of the schematics drawings, Turner et al. envisions entirely different siRNA structures from the presently claimed siNA molecules. Specifically, the Turner et al. molecules are single stranded hairpin siRNA molecules rather than double stranded siNA molecules having two separate oligonucleotide strands. Furthermore, the Turner et al. hairpin siRNA molecules do not have different antisense sequences on separate oligonucleotide strands that are at least partially complementary to one another.

The Office Action fails to explain how the suggested hairpin siRNAs of Turner et al. render the presently claimed siNA molecules obvious. The Office Action merely alleges that Turner et al. teach a multi-target siRNA comprising at least two antisense regions that are complementary to different target genes and that are complementary to sense regions on the

opposite strands (allegedly regions X' and Y' of the instantly claimed molecule). The Office concludes that "as taught by Turner et al., it is possible to target more than one RNA with a single siRNA." Office Action, page 4. No further explanation for obviousness based on Turner et al. is provided. Given the significant differences in the structures of the Turner et al. siRNA molecules versus the presently claimed siNA molecules, it appears that the Office is taking the position that it would have been "obvious to try" to obtain the presently claimed siRNA molecules based on the teachings of Turner et al.

Applicants submit that the presently claimed invention is not obvious in view of Turner et al. for at least two reasons. First, Turner et al. fails to teach or suggest the elements of the presently claimed siNA molecules. Second, application of the "obvious to try" standard is erroneous in the circumstances of this case.

Subsequent to the decision in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727 (2007), the Board of Patent Appeals and Interferences ("BPAI") has continued to recognize the criticality of a finding of all the limitations in a claim to establish a *prima facie* case of obviousness. According to the BPAI:

> [A]n examiner must make "a searching comparison of the claimed invention – *including all its limitations* - with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

Ex Parte Wada, BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished). *See also, Ex parte* Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished).

As discussed *supra*, Turner et al. do not teach or suggest a double stranded nucleic acid molecule with separate strands wherein i) each of the separate strands comprises 24-38 nucleotides, ii) each of the separate strands comprises a sequence that is complementary to a different target sequence (antisense 1 and 2) and iii) the sequences complementary to the different target sequences (antisense 1 and 2) share complementarity with one another in a region comprising 1 to 24 nucleotides (see the Turner et al. hairpin siRNA structures provided *supra*). Thus, Turner et al. fails to show or suggest all of the limitations of the presently claimed siNA molecules.

Further, the Office's presumed position that it would have been "obvious to try" to obtain the presently claimed siRNA molecules based on the teachings of Turner et al. is the improper

standard for an obviousness determination. A proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process (obvious to try); and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success "must be founded in the prior art, not in the applicant's disclosure." *Id.* at 493.

The Federal Circuit has recently clarified the standard for finding obviousness based on an "obvious to try" situation. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" situation to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *Id. See, O'Farrell,* at 903-04. In so doing, the court identified certain circumstances in which a "reasonable expectation of success" is not found and held that the "obvious to try" standard is not appropriate to show obviousness in these circumstances. *In re Kubin*, 561 F.3d at 1360; *In re O'Farrell*, 853 F.2d 894 at 903 (Fed. Cir. 1988). For example, it is improper to hold a claim obvious when:

(1) what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

or

(2) what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Kubin*, 561 F.3d at 1359; *O'Farrell*, 853 F.2d at 903.

Likewise, the Court in *In re Lilly and Co.* indicated that the impermissible "obvious to try" situation exists when "a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would

be obtained if certain directions were pursued". *In re Eli Lilly and Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990).

In contrast, obviousness has been found in instances where the prior art contained detailed enabling methodology for practicing (i.e., making and using) the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful. *O'Farrell*, 853 F.2d at 902; *In re Kubin*, 561 F.3d at 1360.

Application of the "obvious to try" standard is not proper in this case. Although there were general guidelines relating to the design of siRNA for targeting a single gene at the time of filing the instant application, the design of siRNA capable of targeting more than one gene or more than one target site on a single gene was new (and therefore undeveloped) technology. Kubin et al. suggests that one might be able target more than one RNA using a single hairpin siRNA and proposes several hairpin siRNA structures that may or may not be useful in this capacity. However, given that Kubin's disclosure is directed to the production and use of single-stranded hairpin siRNAs, it fails to teach or suggest using a double-stranded siRNA to simultaneously target more than one RNA. In fact, given Kubin's statements regarding the pitfalls of double-stranded RNA (i.e., that it is expensive to synthesize, can be difficult to deliver to certain cells, and has a short-term effect), one skilled in the art would have shied away from pursuing such a molecule.

Moreover, Kubin's disclosure relating to hairpin siRNA molecules fails to teach or provide any guidance whatsoever as to the particular structure, use, and production of the presently claimed double-stranded siNA molecules. As discussed above, Kubin proposes the use of single-stranded hairpin siRNA molecules having two or more antisense sequences that are either on the same strand of the formed duplex or are on opposite strands of the duplex and are complementary to corresponding sense sequences rather than antisense sequences. Such disclosure provides no teaching or guidance for a double-stranded siNA molecule having two antisense sequences that are on opposite strands of the duplex and partially complementary with one another. Given that Kubin et al. fails to teach or suggest the claimed siNA molecules, it certainly fails to provide any enabling methodology for practicing the claimed invention.

Finally, Kubin et al. fail to provide any evidence suggesting that the claimed invention would be successful. Kubin et al. don't test the activity of their proposed hairpin siRNA molecules and therefore don't know whether the hairpin siRNA molecules have RNAi activity

against one or more RNA targets. In view of the fact that Kubin et al. fail to provide evidence suggesting that an siRNA molecule could successfully target more than one RNA, in combination with the lack of teaching relating to the presently claimed siNA molecules, Kubin et al. certainly fail to provide evidence suggesting that the claimed siNA molecules would have RNAi activity against one or more RNA targets.

Therefore, this case is not an instance where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." Rather, it is an instance of exploring a new technology where the prior art provides "only general guidance as to the particular form of the claimed invention or how to achieve it." Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell.* Thus, the pending claims are not *prima facie* obvious over Kubin et al.

None of the other cited references cure the deficiencies of Kubin et al. Although Tuschl, Rana, and Braasch are directed to siRNA, they do not teach or suggest an siRNA targeted to more than one gene or more than one site on a gene, much less teach or suggest the presently claimed siNA molecules. Likewise, Parrish, which is directed to long dsRNA, Pieken and Matulic-Adamic, which are directed to ribozyme technology, and Sullenger, which is directed to antisense technology, fail to teach or suggest an siRNA targeted to more than one RNA, much less teach or suggest the presently claimed siNA molecules. Thus, Turner et a.l, alone, or in combination with Tuschl et al., Rana et al., Parrish et al., Pieken et al., Sullenger et al., Matulic-Adamic et al., Braasch et al., as evidenced by Caplen et al. do not render obvious the claimed invention.

Applicants respectfully request withdrawal of the obviousness rejections.

CONCLUSION

In view of the foregoing remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference would expedite prosecution, she is urged to contact the undersigned before taking further action.

Respectfully submitted,
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